

SJÖGREN'S SYNDROME

Definition

Sjögren's syndrome is a systemic autoimmune disease characterised by dry mouth and dry eyes and various autoimmune changes, confirmed by a blood test or salivary gland biopsy. Sjögren's syndrome can occur as an independent, primary condition, "Primary Sjögren's syndrome", or accompany another autoimmune disease, such as rheumatoid arthritis, in which case it is known as Secondary Sjögren's syndrome. In addition to 1) dryness of the mucous membranes and skin, Sjögren's syndrome can also lead to 2) general symptoms such as fatigue, musculoskeletal pain and less commonly 3) pathological changes in internal organs and 4) various complications such as caries, candidosis, congenital heart block and lymphoma.

Epidemiology

Sjögren's syndrome is considered to be one of the commonest autoimmune diseases but there is no consensus as to how many sufferers there are worldwide. One of the problems, in estimating exact numbers, is that many different criteria have been used to diagnose Sjögren's syndrome at different times and in different countries. In addition, many sufferers probably do not seek professional advice about their condition or it is not recognised by health care professionals. It has been reported that Sjögren's syndrome affects between 0.04-4.8% of the population and this includes patients with rheumatoid arthritis, one third of whom develop the secondary form. Sjögren's syndrome is much more common in women (only 1 in 10 are men) and usually presents between the ages of 40 and 60 years.

Clinical presentation

The most common symptoms of patients with Sjögren's syndrome relate to dryness of the eyes and/or mouth. Saliva lubricates the mouth and has an important role in protecting against candidal infections (thrush) and dental caries (decay). As the salivary glands are directly involved in Sjögren's syndrome, they may become swollen or develop infections. Patients with a reduced flow of saliva frequently complain of difficulty or soreness when eating and/or speaking and notice that their taste is affected. Swallowing may be difficult and frequent sips of water are often required; occasionally there is hoarseness of the voice. Dryness of the eyes can result in a feeling of "irritable" or "gritty eyes" and strong lights may cause discomfort. An accumulation of mucous or debris can result in "sticky" eyes and recurrent eye infections. Dryness may also affect other sites in the body, such as the skin, and vaginal dryness can result in painful or difficult sexual intercourse. All these problems can severely compromise a patient's quality of life. Another common complaint of patients with Sjögren's syndrome is feeling more tired than usual and this lethargy may prompt patients to seek medical advice. Sjögren's syndrome is also characterised by joint (and muscle) pain, which is known as arthralgia (and myalgia), typically affecting the hand,

wrist and foot joints but with no accompanying swelling. The third most common general symptom of Sjögren's syndrome is Raynaud's phenomenon, in which the fingers feel cold and turn white. Occasionally patients with Sjögren's syndrome seek medical attention because of other symptoms resulting from involvement of the skin, thyroid gland, stomach, bowel, liver, lungs, kidneys and bladder. Other organs, such as the nervous system, are probably less commonly involved. Sjögren's syndrome may also have haematological manifestations which may be diagnosed when routine blood tests are carried out and reveal changes such as anaemia or raised erythrocyte sedimentation rate (inflammatory marker in the blood), which prompt further investigation.

Etiopathogenesis

The exact cause of Sjögren's syndrome is unknown. The consensus opinion at the present time is that an environmental factor, such as a yet unknown virus, triggers an abnormal immune reaction. In Sjögren's syndrome, as in other autoimmune disorders the body reacts against itself, with an exaggerated immunological response, which appears to affect regulatory molecules in cells and tissues. This inappropriate response can lead to an accumulation of inflammatory cells in the salivary or tear (lacrimal) glands and the production of autoantibodies, which can be demonstrated in a blood sample. The mechanism, by which the function of glands is reduced has yet to be worked out. Although Sjögren's syndrome is not uncommon, relatively few people develop the disease and it is therefore likely that those affected have an inherent genetic susceptibility. It is rare, however, for Sjögren's syndrome to be passed from mother to daughter, and familial cases are the subject of ongoing investigations. The female preponderance of Sjögren's syndrome, particularly in the mature women, suggests that a gender-linked susceptibility – possibly related to diminished or altered production of sex hormones may be involved.

Diagnosis

The European-American consensus criteria for the diagnosis of Sjögren's syndrome have now been agreed and are presented in Table 1. It should be emphasised that the symptoms and clinical findings do not appear overnight and that a definite diagnosis of Sjögren's according to these criteria is not necessary for treatment of troublesome symptoms and complications.

Sicca syndrome

A diagnosis of this is sometimes given to patients who have dryness of their eyes and/or mouth but do not have the objective signs or immunological markers necessary for the diagnosis of Sjögren's syndrome. Sicca means dry(ness) and may be a result of other illnesses (e.g. depression) affecting the functioning of glands and radiotherapy for cancer, or the treatment of thyroid disease. A large number of drugs (e.g. antidepressants) can cause sicca symptoms. Symptomatic treatment for sicca symptoms is similar to that available for Sjögren's syndrome.

Treatment

At the present time, there is no curative treatment for Sjögren's syndrome, but symptoms and complications can be effectively managed by the local (topical) therapy and/or drugs taken systemically. Dryness of the mouth and eyes can be managed by either stimulating the existing function of the saliva or tear producing glands or by providing substitute secretions, e.g. saliva or artificial tears. Some of the locally used drugs contain active substances, like mucolytic or anti-inflammatory agents, vitamin A, topical estrogens etc. The severity of disease, degree of organ involvement and type of symptoms together with the preference of patients will dictate the management of Sjögren's syndrome.

Dry Mouth

- Stimulate salivary gland function by regularly chewing sugar-free gum, sweets or pastilles.
- Sip water or suck ice cubes.
- Use artificial saliva or replacement gels as required.
- Candida (thrush infection) in the mouth should be promptly treated.
- Visit your dentist regularly and seek advice on appropriate diet (for example avoid sweet foods) and the maintenance of good dental hygiene. Fluoride supplements and chlorhexidine may be indicated.
- The use of a systemic drug known as a "secretagogue", e.g. pilocarpine or cevimeline, which stimulates any residual glandular function may be indicated, if topical therapy is not effective for dry mouth (or eyes).

Dry Eyes

- Seek professional advice concerning the use of tear substitutes (eye drops, gels and ointments).
- Artificial tears should be preservative free, particularly if used on a frequent basis.
- Mucolytic drops such as acetylcysteine may be helpful if mucous threads ("sticky eyes") are a problem.
- Pilocarpine or cevimeline may be beneficial (see above).
- Consider use of moisture-retaining spectacles, e.g. swimming goggles and room humidifiers.
- Conservation of tears by blocking their natural drainage may be indicated. Temporary punctal plugs are inserted and if beneficial the tear ducts (canaliculi) can be surgically closed.

Dryness in Other Sites

- Vaginal dryness – use moisturising gels or pessaries for lubrication, particularly if intercourse is difficult or painful. Occasionally, topical or systemic hormone replacement can be helpful.
- Ask your doctor, or pharmacist, for advice about managing dryness of other mucous membranes, e.g. the throat.
- Use moisturising creams and emollients for dryness of the skin and lips.
- Avoid dry, smoke-filled environments.

General Manifestations of SS

- Excessive fatigue should be investigated to eliminate other systemic causes (e.g. anaemia or thyroid disease).
- Joint and muscle pain can be treated symptomatically with analgesics (pain killers), such as paracetamol (acetoaminophen) or a non-steroidal anti-inflammatory drug.
- For severe joint pain or extreme fatigue, your doctor may recommend hydroxychloroquine, or less commonly, a glucocorticosteroid.
- White fingers (Raynaud's phenomenon) may respond to a vasodilator drug, which is usually a calcium blocking agent.
- Drugs which directly affect the immune system, (known as "immunomodulatory" drugs), may be considered in cases where there is significant organ involvement. Drugs, such as methotrexate, azathioprine or ciclosporin have potentially serious side effects which must be considered when assessing their potential benefits for Sjögren's syndrome.
- Effective management sometimes necessitates replacement therapy, e.g. thyroid hormone in hypothyroidism and vitamin B12 in chronic atrophic gastritis. In primary biliary cirrhosis, non-irritating bile acid ursodeoxycholic acid is used to substitute for irritating endogenous bile acids and in interstitial cystitis the defective, protective, layer of the urinary bladder can be replaced by proteoglycans. Renal tubular acidosis can be treated with sodium bicarbonate and diuretic drugs which diminish calcium secretion and reduce the risk of developing kidney stones. (582 words)

Prognosis and Complications

Sjögren's syndrome is a chronic disease which usually runs in cycles and does not usually lead to serious incapacity or invalidity. Patients with Sjögren's syndrome may, however, have a diminished quality of life because of mucosal dryness, fatigue and aching muscles and joints. Occasionally patients with Sjögren's syndrome become depressed, but this tends to be a feature of many other chronic illnesses as well. One of the most distressing and frustrating aspects of Sjögren's syndrome for patients is that the diagnosis of their disease may be delayed for up to ten years from the onset of symptoms. Due to the rather diverse nature of symptoms in Sjögren's syndrome, patients may present to a wide range of differing specialties (including oral medicine/surgery, rheumatology, ophthalmology and ENT specialists) and may not be diagnosed during the early stages of the disease. It is, therefore, important that the health care professionals and the general public are aware of this condition which should be suspected if anyone complains of a persistently dry mouth and/or eyes. Most complications of Sjögren's syndrome can be prevented or managed by early institution of local and systemic (if appropriate) treatment. Early recognition of rampant caries (dental decay) is important to prevent long-term damage to the teeth and avoid the provision of dental prostheses (false teeth). Recurrent oral candidosis (thrush infection) can be treated by local or systemic antifungal medication. Dryness of the eyes, if appropriately treated by the use of

artificial tear substitutes or punctal occlusion, rarely leads to permanent scarring of the ocular surfaces or ulceration of the cornea. Severe joint injury and destruction are rare in Sjögren's syndrome except for those secondary cases which are associated with rheumatoid arthritis. If involvement of internal organs is detected early, serious complications are uncommon.

There are two specific complications of Sjögren's syndrome that merit special consideration, one is a significant but small risk of developing lymphoma and the other is a potential but small risk of heart block in babies born to mothers with Primary Sjögren's syndrome. Although the risk for lymphoma has been estimated to be over 40 times higher in Sjögren's syndrome than the general population the actual risk is still modest. Lymphoma is a malignancy occurring in the lymph nodes or collections of lymphoid tissue elsewhere in the body. Lymphomas may arise in the salivary glands of patients with Sjögren's syndrome and are known as "MALTomas" (from the mucosal associated lymphoid tissue). If patients develop persistently enlarged salivary glands, particularly if the parotids significantly increase in size, then a more detailed examination of the glands is required (e.g. ultrasound, CT scan or MRI examination and biopsy – usually a fine needle aspiration). Other systemic features such as slight fever, unexplained weight loss and progressive fatigue should be investigated; there may also be a change in the immunological markers in the blood. It is important to emphasise that the risk of developing lymphoma in Sjögren's syndrome is still extremely low and some types of lymphomas, e.g. gastric lymphoma, can be treated with simple eradication of *Helicobacter pylori*.

It is thought that the rare complication of congenital lupus skin eruption and heart block in the unborn or new born children of patients with Sjögren's syndrome is the result of maternal antibodies crossing the placenta. However, currently the exact identity and mechanism of action of these antibodies is unknown. Irrespective of the mechanism it is known that the development of the conduction system within the heart is disturbed and the baby may be born with heart block, which may require a pacemaker at birth. For this reason, women suffering from Sjögren's syndrome should be carefully monitored during pregnancy and monitored in hospital units with paediatric expertise in preventing, diagnosing and treating intrauterine or neonatal heart disturbances.

Prevention

In the light of current knowledge the cause of Sjögren's syndrome remains unknown and therefore prevention is not possible. Many of the complications of Sjögren's syndrome may however be prevented or symptoms satisfactorily controlled by the strategies already discussed. Early recognition is the key to preventing many of the long-term complications of Sjögren's syndrome and it is important that patients with multi-system involvement are treated by a team of health care professionals. Hypothyroidism, interstitial pneumonias, celiac disease and chronic atrophic gastritis are relatively common in Sjögren's syndrome and can, when suspected, be easily diagnosed and treated before any permanent changes result.

Patients with Sjögren's syndrome, like the rest of the population, should strive to maintain a healthy lifestyle with a balanced diet and regular exercise; tobacco smoking and excessive alcohol consumption are best avoided.

Many European countries now have patient support groups for patients with Sjögren's syndrome; these provide mutual support and helpful advice for coping with symptoms and improving quality of life.

Table 1. Revised international classification criteria for Sjögren's syndrome

(Vitali C, Bombardieri S, Jonson R et al (2002). Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group)

I Ocular symptoms: a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1. Schirmer's test performed without anaesthesia (≤ 5 mm in 5 minutes).
2. Rose bengal score or other ocular dye score (≥ 4 according to van Bijsterveld's scoring system).

IV Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1 , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.

V Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (≤ 1.5 ml in 15 minutes).
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts.
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer.

VI Autoantibodies: presence in the serum of the following autoantibodies:

1. Antibodies to Ro (SS-A) or La (SS-B) antigens, or both.

For the diagnosis of Primary SS:

In patients without any potentially associated disease, primary SS may be defined as follows:

- a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive.
 - b. The presence of any 3 of the 4 objective criteria items (that, is items III, IV, V, VI).
 - c. The classification tree procedure represents a valid alternative method of classification, although it should be more properly used in clinical-epidemiological survey.
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For the diagnosis of Secondary SS:

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV and V may be considered as indicative of secondary SS.

Exclusion criteria:

Past head and neck radiation treatment

Hepatitis C infection

Acquired immunodeficiency disease (AIDS)

Pre-existing lymphoma

Sarcoidosis

Graft versus host disease

Use of anticholinergic drugs (since a time shorter than 3-fold the half life of the drug).

Additional information about investigations

- 1 Schirmer's test: a small piece of blotting paper is inserted into the eye to measure tear production.
 - 2 Rose Bengal test: an eye specialist will place eye drops containing dye (e.g. Rose Bengal or Lissamine green) and examine the surface of the eye, using an instrument called a "slit-lamp".
 - 3 Lip biopsy: a small (minor) salivary gland can be surgically removed from inside the lower lip, under local anaesthesia. This is examined under a microscope to look for changes suggestive of Sjögren's syndrome.
 - 4 Assessment of salivary gland function: this includes measurement of saliva flow (e.g. by spitting into a container) or injecting a labelled substance (isotope) into a vein or contrast dye into the salivary gland ducts which empty into the mouth. (689 words)
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Pictures

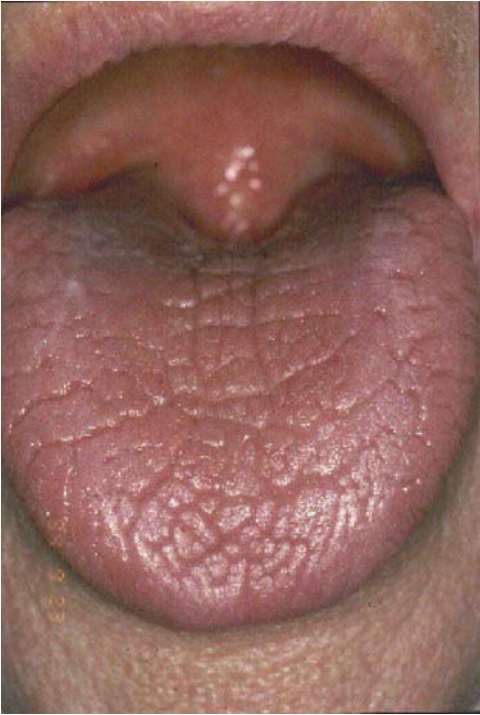


Figure 1. Dry lobulated tongue



Figure 2. No pooling of saliva on the floor of the mouth

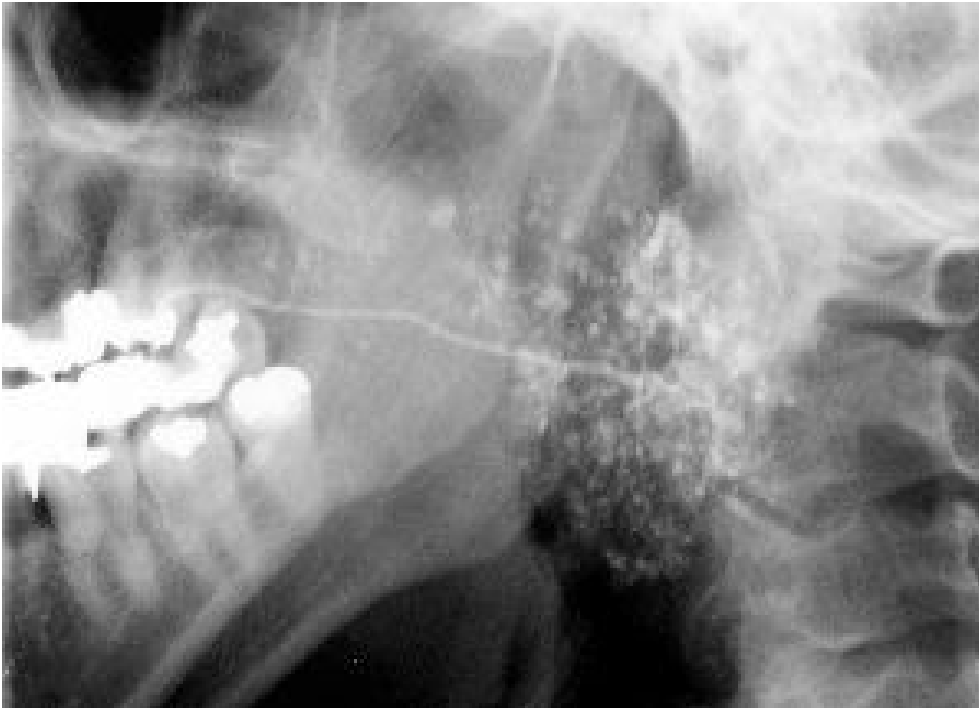


Figure 3. Primary Sjögren's syndrome: sialography



Figure 4. Primary Sjögren's syndrome: dental decay



Figure 5. Primary Sjögren's syndrome: parotid gland swelling



Figure 6. Primary Sjögren's syndrome: infected parotid gland –pus from duct

Further reading

- 1 Vitali C, Bombardieri S et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61:554-8
- 2 Sjögren's syndrome. A concise guide to diagnosis and management for health professionals. The British Sjögren's syndrome Association.
- 3 Jonsson R, Haga H-J, Gordon T: Sjögren's syndrome. In: *Arthritis and Allied Conditions – A Textbook of Rheumatology*, Koopman WJ , ed 14th Edition. Lippincott Williams & Wilkins, Philadelphia, 2001, pp 1736-1759.

Links

Sjögren's syndrome Foundation www.sjogrens.org/

British Sjögren's Syndrome Ass. <http://ourworld.compuserve.com/homepages/bssassociation>